XYREM- sodium oxybate solution
Jazz Pharmaceuticals, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use XYREM safely and effectively. See full prescribing information for XYREM.

XYREM® (sodium oxybate) oral solution, CIII
Initial U.S. Approval: 2002

WARNING: CENTRAL NERVOUS SYSTEM (CNS) DEPRESSION and MISUSE AND ABUSE.

See full prescribing information for complete boxed warning.

- **Respiratory depression can occur with Xyrem use (5.4)**
- **Xyrem is a Schedule III controlled substance and is the sodium salt of gamma hydroxybutyrate (GHB), a Schedule I controlled substance. Abuse or misuse of illicit GHB is associated with CNS adverse reactions, including seizure, respiratory depression, decreased consciousness, coma and death (5.2, 9.2)**
- **Because of the risks of CNS depression, abuse, and misuse, Xyrem is available only through a restricted distribution program called the Xyrem REMS Program using the central pharmacy that is specially certified. Prescribers and patients must enroll in the program. (5.3)**

RECENT MAJOR CHANGES

Boxed Warning, Xyrem REMS Program	04/2015
Indications and Usage, Xyrem REMS Program (1)	04/2015
Dosage and Administration, Dose Adjustment with Co-administration of Divalproex Sodium (2.4)	04/2014
Warnings and Precautions, Xyrem REMS Program required components (5.3)	04/2015

INDICATIONS AND USAGE

Xyrem is a central nervous system depressant indicated for the treatment of:

- Cataplexy in narcolepsy (1.1)
- Excessive daytime sleepiness (EDS) in narcolepsy (1.2)

Xyrem may only be dispensed to patients enrolled in the Xyrem REMS Program (1).

DOSAGE AND ADMINISTRATION

- Initiate dose at 4.5 grams (g) per night administered orally in two equal, divided doses: 2.25 g at bedtime and 2.25 g taken 2.5 to 4 hours later (2.1)
- Titrate to effect in increments of 1.5 g per night at weekly intervals (0.75 g at bedtime and 0.75 g taken 2.5 to 4 hours later) (2.1).
- Recommended dose range: 6 g to 9 g per night orally (2.1).

Total Nightly Dose	Take at Bedtime	Take 2.5 to 4 Hours Later
4.5 g per night	2.25 g	2.25 g
6 g per night	3 g	3 g
7.5 g per night	3.75 g	3.75 g
9 g per night	4.5 g	4.5 g

- Take each dose while in bed and lie down after dosing (2.2).
- Allow 2 hours after eating before dosing (2.2).
- Prepare both doses prior to bedtime; dilute each dose with approximately ¼ cup of water in pharmacy-provided vials (2.2).
- Patients with Hepatic Impairment: starting dose is 2.25 g per night administered orally in two equal, divided doses of approximately 1.13 g at bedtime and approximately 1.13 g taken 2.5 to 4 hours later (2.3).
- Concomitant use with divalproex sodium: an initial reduction in Xyrem dose of at least 20% is recommended (2.4,

7.2).

DOSAGE FORMS AND STRENGTHS

Oral solution, 0.5 g per mL (3)

CONTRAINDICATIONS

- Succinic semialdehyde dehydrogenase deficiency (4)
- In combination with sedative hypnotics or alcohol (4)

WARNINGS AND PRECAUTIONS

- CNS depression: Use caution when considering the concurrent use of Xyrem with other CNS depressants (5.1).
- Caution patients against hazardous activities requiring complete mental alertness or motor coordination within the first 6 hours of dosing or after first initiating treatment until certain that Xyrem does not affect them adversely (5.1).
- Depression and suicidality: Monitor patients for emergent or increased depression and suicidality (5.5).
- Confusion/Anxiety: Monitor for impaired motor/cognitive function (5.6).
- Parasomnias: Evaluate episodes of sleepwalking (5.7).
- High sodium content in Xyrem: Monitor patients with heart failure, hypertension, or impaired renal function (5.8).

ADVERSE REACTIONS

Most common adverse reactions (≥ 5% and at least twice the incidence with placebo) were nausea, dizziness, vomiting, somnolence, enuresis, and tremor (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Jazz Pharmaceuticals at 1-800-520-5568, or FDA at 1-800-FDA-1088 or www.fda.gov/Medwatch.

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm (8.1).
- Geriatric patients: Monitor for impaired motor and/or cognitive function when taking Xyrem (8.5).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 4/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: CENTRAL NERVOUS SYSTEM DEPRESSION and MISUSE AND ABUSE.

Xyrem (sodium oxybate) is a CNS depressant. In clinical trials at recommended doses obtundation and clinically significant respiratory depression occurred in Xyrem-treated patients. Almost all of the patients who received Xyrem during clinical trials in narcolepsy were receiving central nervous system stimulants *[see Warnings and Precautions (5.1)]*.

Xyrem® (sodium oxybate) is the sodium salt of gamma hydroxybutyrate (GHB). Abuse of GHB, either alone or in combination with other CNS depressants, is associated with CNS adverse reactions, including seizure, respiratory depression, decreases in the level of consciousness, coma, and death *[see Warnings and Precautions (5.2)].*

Because of the risks of CNS depression, abuse, and misuse, Xyrem is available only through a restricted distribution program called the Xyrem REMS Program, using the central pharmacy that is specially certified. Prescribers and patients must enroll in the program. For further information go to www.XYREMREMS.com or call 1-866-XYREM88® (1-866-997-3688). *[see Warnings and Precautions (5.3)].*

1 INDICATIONS AND USAGE

Limitations of Use

Xyrem may only be dispensed to patients enrolled in the Xyrem REMS Program *[see Warnings and Precautions (5.3)]*.

1.1 Cataplexy in Narcolepsy

Xyrem (sodium oxybate) oral solution is indicated for the treatment of cataplexy in narcolepsy.

1.2 Excessive Daytime Sleepiness in Narcolepsy

Xyrem (sodium oxybate) oral solution is indicated for the treatment of excessive daytime sleepiness (EDS) in narcolepsy.

2 DOSAGE AND ADMINISTRATION

Healthcare professionals who prescribe Xyrem must enroll in the Xyrem REMS Program and must comply with the requirements to ensure safe use of Xyrem *[see Warnings and Precautions (5.3)]*.

2.1 Dosing Information

The recommended starting dose is 4.5 grams (g) per night administered orally in two equal, divided doses: 2.25 g at bedtime and 2.25 g taken 2.5 to 4 hours later (see Table 1). Increase the dose by 1.5 g per night at weekly intervals (additional 0.75 g at bedtime and 0.75 g taken 2.5 to 4 hours later) to the effective dose range of 6 g to 9 g per night orally. Doses higher than 9 g per night have not been studied and should not ordinarily be administered.

Table 1: Xyrem Dose Regimen (g = grams)

If A Patient's Total Nightly Dose is:	Take at Bedtime:	Take 2.5 to 4 Hours Later:
4.5 g per night	2.25 g	2.25 g
6 g per night	3 g	3 g
7.5 g per night	3.75 g	3.75 g
9 g per night	4.5 g	4.5 g

2.2 Important Administration Instructions

Take the first dose of Xyrem at least 2 hours after eating because food significantly reduces the bioavailability of sodium oxybate.

Prepare both doses of Xyrem prior to bedtime. Prior to ingestion, each dose of Xyrem should be diluted with approximately ¼ cup (approximately 60 mL) of water in the empty pharmacy vials provided. Patients should take both doses of Xyrem while in bed and lie down immediately after dosing as Xyrem may cause them to fall asleep abruptly without first feeling drowsy. Patients will often fall asleep within 5 minutes of taking Xyrem, and will usually fall asleep within 15 minutes, though the time it takes any individual patient to fall asleep may vary from night to night. Patients should remain in bed following ingestion of the first and second doses, and should not take the second dose until 2.5 to 4 hours after the first dose. Patients may need to set an alarm to awaken for the second dose. Rarely, patients may take up to 2 hours to fall asleep.

2.3 Dose Modification in Patients with Hepatic Impairment

The recommended starting dose in patients with hepatic impairment is 2.25 g per night administered orally in two equal, divided doses: approximately 1.13 g at bedtime and approximately 1.13 g taken 2.5 to 4 hours later *[see Use in Specific Populations (8.6); Clinical Pharmacology (12.3)]*.

2.4 Dose Adjustment with Co-administration of Divalproex Sodium

Pharmacokinetic and pharmacodynamic interactions have been observed when Xyrem is co-administered with divalproex sodium. For patients already stabilized on Xyrem, it is recommended that addition of divalproex sodium should be accompanied by an initial reduction in the nightly dose of Xyrem by at least 20%. For patients already taking divalproex sodium, it is recommended that prescribers use a lower starting Xyrem dose with introducing Xyrem. Prescribers should monitor patient response and adjust dose accordingly [*see Drug Interactions (7.2)* and *Clinical Pharmacology (12.3)*].

3 DOSAGE FORMS AND STRENGTHS

Xyrem is a clear to slightly opalescent oral solution, in a concentration of 0.5 g per mL.

4 CONTRAINDICATIONS

- Xyrem is contraindicated in patients being treated with sedative hypnotic agents.
- Patients should not drink alcohol when using Xyrem.
- Xyrem is contraindicated in patients with succinic semialdehyde dehydrogenase deficiency. This is a rare disorder of inborn error of metabolism variably characterized by mental retardation, hypotonia, and ataxia.

5 WARNINGS AND PRECAUTIONS

5.1 Central Nervous System Depression

Xyrem is a central nervous system (CNS) depressant. Alcohol and sedative hypnotics are contraindicated in patients who are using Xyrem. The concurrent use of Xyrem with other CNS depressants, including but not limited to opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, sedating anti-epileptic drugs, general anesthetics, muscle relaxants, and/or illicit CNS depressants, may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death. If use of these CNS depressants in combination with Xyrem is required, dose reduction or discontinuation of one or more CNS depressants (including Xyrem) should be considered. In addition, if short-term use of an opioid (e.g. post- or perioperative) is required, interruption of treatment with Xyrem should be considered.

Healthcare providers should caution patients about operating hazardous machinery, including automobiles or airplanes, until they are reasonably certain that Xyrem does not affect them adversely (e.g., impair judgment, thinking, or motor skills). Patients should not engage in hazardous occupations or activities requiring complete mental alertness or motor coordination, such as operating machinery or a motor vehicle or flying an airplane, for at least 6 hours after taking the second nightly dose of Xyrem. Patients should be queried about CNS depression-related events upon initiation of Xyrem therapy and periodically thereafter *[see Warnings and Precautions (5.3)]*.

5.2 Abuse and Misuse

Xyrem is a Schedule III controlled substance. The active ingredient of Xyrem, sodium oxybate or gamma-hydroxybutyrate (GHB), is a Schedule I controlled substance. Abuse of illicit GHB, either alone or in combination with other CNS depressants, is associated with CNS adverse reactions, including seizure, respiratory depression, decreases in the level of consciousness, coma, and death. The rapid onset of sedation, coupled with the amnestic features of Xyrem, particularly when combined with alcohol, has proven to be dangerous for the voluntary and involuntary user (e.g., assault victim). Because illicit use and abuse of GHB have been reported, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of GHB (e.g. increase in size or frequency of dosing, drug-seeking behavior, feigned cataplexy) *[see Warnings and Precautions (5.3)* and *Drug Abuse and Dependence (9.2)]*.

5.3 Xyrem REMS Program

Because of the risks of central nervous system depression and abuse/misuse, Xyrem is available only through a restricted distribution program called the Xyrem REMS Program.

Required components of the Xyrem REMS Program include:

- Healthcare Providers who prescribe Xyrem are specially certified
- Xyrem will be dispensed only by the central pharmacy that is specially certified
- Xyrem will be dispensed and shipped only to patients who are enrolled in the XYREM REMS Program with documentation of safe use

Further information is available at www.XYREMREMS.com or **1-866-XYREM88® (1-866-997-3688)**.

5.4 Respiratory Depression and Sleep-Disordered Breathing

Xyrem may impair respiratory drive, especially in patients with compromised respiratory function. In overdoses, life-threatening respiratory depression has been reported *[see Overdosage (10)]*.

In a study assessing the respiratory-depressant effects of Xyrem at doses up to 9 g per night in 21 patients with narcolepsy, no dose-related changes in oxygen saturation were demonstrated in the group as a whole. One of the four patients with preexisting, moderate-to-severe sleep apnea had significant worsening of the apnea/hypopnea index during treatment.

In a study assessing the effects of Xyrem 9 g per night in 50 patients with obstructive sleep apnea, Xyrem did not increase the severity of sleep-disordered breathing and did not adversely affect the average duration and severity of oxygen desaturation overall. However, there was a significant increase in the number of central apneas in patients taking Xyrem, and clinically significant oxygen desaturation ($\leq$ 55%) was measured in three patients (6%) after Xyrem administration, with one patient withdrawing from the study and two continuing after single brief instances of desaturation. Prescribers should be aware that increased central apneas and clinically relevant desaturation events have been observed with Xyrem administration.

In clinical trials in 128 patients with narcolepsy, two subjects had profound CNS depression, which

resolved after supportive respiratory intervention. Two other patients discontinued sodium oxybate because of severe difficulty breathing and an increase in obstructive sleep apnea. In two controlled trials assessing polysomnographic (PSG) measures in patients with narcolepsy, 40 of 477 patients were included with a baseline apnea/hypopnea index of 16 to 67 events per hour, indicative of mild to severe sleep-disordered breathing. None of the 40 patients had a clinically significant worsening of respiratory function as measured by apnea/hypopnea index and pulse oximetry at doses of 4.5 g to 9 g per night.

Prescribers should be aware that sleep-related breathing disorders tend to be more prevalent in obese patients and in postmenopausal women not on hormone replacement therapy as well as among patients with narcolepsy.

5.5 Depression and Suicidality

In clinical trials in patients with narcolepsy (n=781), there were two suicides and two attempted suicides in Xyrem-treated patients, including three patients with a previous history of depressive psychiatric disorder. Of the two suicides, one patient used Xyrem in conjunction with other drugs. Xyrem was not involved in the second suicide. Adverse reactions of depression were reported by 7% of 781 Xyrem-treated patients, with four patients (< 1%) discontinuing because of depression. In most cases, no change in Xyrem treatment was required.

In a controlled trial, with patients randomized to fixed doses of 3 g, 6 g, or 9 g per night Xyrem or placebo, there was a single event of depression at the 3 g per night dose. In another controlled trial, with patients titrated from an initial 4.5 g per night starting dose, the incidences of depression were 1 (1.7%), 1 (1.5%), 2 (3.2%), and 2 (3.6%) for the placebo, 4.5 g, 6 g, and 9 g per night doses, respectively.

The emergence of depression in patients treated with Xyrem requires careful and immediate evaluation. Patients with a previous history of a depressive illness and/or suicide attempt should be monitored carefully for the emergence of depressive symptoms while taking Xyrem.

5.6 Other Behavioral or Psychiatic Adverse Reactions

During clinical trials in narcolepsy, 3% of 781 patients treated with Xyrem experienced confusion, with incidence generally increasing with dose.

Less than 1% of patients discontinued the drug because of confusion. Confusion was reported at all recommended doses from 6 g to 9 g per night. In a controlled trial where patients were randomized to fixed total daily doses of 3 g, 6 g, or 9 g per night or placebo, a dose-response relationship for confusion was demonstrated, with 17% of patients at 9 g per night experiencing confusion. In all cases in that controlled trial, the confusion resolved soon after termination of treatment. In Trial 3 where sodium oxybate was titrated from an initial 4.5 g per night dose, there was a single event of confusion in one patient at the 9 g per night dose. In the majority of cases in all clinical trials in narcolepsy, confusion resolved either soon after termination of dosing or with continued treatment. However, patients treated with Xyrem who become confused should be evaluated fully, and appropriate intervention considered on an individual basis.

Anxiety occurred in 5.8% of the 874 patients receiving Xyrem in clinical trials in another population. The emergence of or increase in anxiety in patients taking Xyrem should be carefully monitored.

Other neuropsychiatric reactions reported in Xyrem clinical trials included hallucinations, paranoia, psychosis, and agitation. The emergence of thought disorders and/or behavior abnormalities requires careful and immediate evaluation.

5.7 Parasomnias

Sleepwalking, defined as confused behavior occurring at night and at times associated with wandering, was reported in 6% of 781 patients with narcolepsy treated with Xyrem in controlled and long-term

open-label studies, with < 1% of patients discontinuing due to sleepwalking. Rates of sleepwalking were similar for patients taking placebo and patients taking Xyrem in controlled trials. It is unclear if some or all of the reported sleepwalking episodes correspond to true somnambulism, which is a parasomnia occurring during non-REM sleep, or to any other specific medical disorder. Five instances of significant injury or potential injury were associated with sleepwalking during a clinical trial of Xyrem in patients with narcolepsy.

Parasomnias including sleepwalking have been reported in postmarketing experience with Xyrem. Therefore, episodes of sleepwalking should be fully evaluated and appropriate interventions considered.

5.8 Use in Patients Sensitive to High Sodium Intake

Xyrem has a high salt content. In patients sensitive to salt intake (e.g., those with heart failure, hypertension, or renal impairment) consider the amount of daily sodium intake in each dose of Xyrem. Table 2 provides the approximate sodium content per Xyrem dose.

Table 2

Approximate Sodium Content per Total Nightly Dose of Xyrem (g = grams)

Xyrem Dose	Sodium Content/Total Nightly Exposure
3 g per night	550 mg
4.5 g per night	820 mg
6 g per night	1100 mg
7.5 g per night	1400 mg
9 g per night	1640 mg

6 ADVERSE REACTIONS

The following adverse reactions appear in other sections of the labeling:

- CNS depression *[see Warnings and Precautions (5.1)]*
- Abuse and Misuse *[see Warnings and Precautions (5.2)]*
- Respiratory Depression and Sleep-disordered Breathing *[see Warnings and Precautions (5.4)]*
- Depression and Suicidality *[see Warnings and Precautions (5.5)]*
- Other Behavioral or Psychiatric Adverse Reactions *[see Warnings and Precautions (5.6)]*
- Parasomnias *[see Warnings and Precautions (5.7)]*
- Use in Patients Sensitive to High Sodium Intake *[see Warnings and Precautions (5.8)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Xyrem was studied in three placebo-controlled clinical trials (Trials N1, N3, and N4, described in Sections 14.1 and 14.2) in 611 patients with narcolepsy (398 subjects treated with Xyrem, and 213 with placebo). A total of 781 patients with narcolepsy were treated with Xyrem in controlled and uncontrolled clinical trials.

Section 6.1 and Table 3 presents adverse reactions from three pooled, controlled trials (N1, N3, N4) in patients with narcolepsy.

Adverse Reactions Leading to Treatment Discontinuation:

Of the 398 Xyrem-treated patients with narcolepsy, 10.3% of patients discontinued because of adverse reactions compared with 2.8% of patients receiving placebo. The most common adverse reaction leading to discontinuation was nausea (2.8%). The majority of adverse reactions leading to discontinuation began during the first few weeks of treatment.

Commonly Observed Adverse Reactions in Controlled Clinical Trials:

The most common adverse reactions (incidence ≥ 5% and twice the rate seen with placebo) in Xyrem-treated patients were nausea, dizziness, vomiting, somnolence, enuresis, and tremor.

Adverse Reactions Occurring at an Incidence of 2% or greater:

Table 3 lists adverse reactions that occurred at a frequency of 2% or more in any treatment group for three controlled trials and were more frequent in any Xyrem treatment group than with placebo. Adverse reactions are summarized by dose at onset. Nearly all patients in these studies initiated treatment at 4.5 g per night. In patients who remained on treatment, adverse reactions tended to occur early and to diminish over time.

Table 3
Adverse Reactions Occurring in ≥2% of Patients and More Frequently with Xyrem than Placebo in Three Controlled Trials (N1, N3, N4) by Body System and Dose at Onset

System Organ Class/MedDRA Preferred Term	Placebo (n=213) %	Xyrem 4.5g (n=185) %	Xyrem 6g (n=258) %	Xyrem 9g (n=178) %
ANY ADVERSE REACTION	62	45	55	70
GASTROINTESTINAL DISORDERS				
Nausea	3	8	13	20
Vomiting	1	2	4	11
Diarrhea	2	4	3	4
Abdominal pain upper	2	3	1	2
Dry mouth	2	1	2	1
GENERAL DISORDERS AND ADMINISTRATIVE SITE CONDITIONS				
Pain	1	1	< 1	3
Feeling drunk	1	0	< 1	3
Edema peripheral	1	3	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				
Pain in extremity	1	3	1	1
Cataplexy	1	1	1	2
Muscle spasms	2	2	< 1	2
NERVOUS SYSTEM DISORDERS				
Dizziness	4	9	11	15
Somnolence	4	1	3	8
Tremor	0	0	2	5
Paresthesia	1	2	1	3
Disturbance in attention	0	1	0	4
Sleep paralysis	1	0	1	3
PSYCHIATRIC DISORDERS				
Disorientation	1	1	2	3
Anxiety	1	1	1	2
Irritability	1	0	< 1	3
Sleep walking	0	0	0	3
RENAL AND URINARY DISORDERS				

Enuresis	1	3	3	7
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
Hyperhidrosis	0	1	1	3

Dose-Response Information

In clinical trials in narcolepsy, a dose-response relationship was observed for nausea, vomiting, paresthesia, disorientation, irritability, disturbance in attention, feeling drunk, sleepwalking, and enuresis. The incidence of all these reactions was notably higher at 9 g per night.

In controlled trials in narcolepsy, discontinuations of treatment due to adverse reactions were greater at higher doses of Xyrem.

6.2 Postmarketing Experience

The following additional adverse reactions that have a likely causal relationship to Xyrem exposure have been identified during postmarketing use of Xyrem. These adverse reactions include: arthralgia, decreased appetite, fall, fluid retention, hangover, headache, hypersensitivity, hypertension, memory impairment, panic attack, vision blurred, and weight decreased. Because these reactions are reported voluntarily, it is not always possible to reliably estimate their frequency.

7 DRUG INTERACTIONS

7.1 Alcohol, Sedative Hypnotics, and CNS Depressants

Xyrem should not be used in combination with alcohol or sedative hypnotics. Use of other CNS depressants may potentiate the CNS-depressant effects of Xyrem.

7.2 Divalproex Sodium

Concomitant use of Xyrem with divalproex sodium resulted in a 25% mean increase in systemic exposure to Xyrem (AUC ratio range of 0.8 to 1.7) and in a greater impairment on some tests of attention and working memory. An initial Xyrem dose reduction of at least 20% is recommended if divalproex sodium is prescribed to patients already taking Xyrem *[see Dosage and Administration (2.4)* and *Clinical Pharmacology (12.3)]*. Prescribers are advised to monitor patient response closely and adjust dose accordingly if concomitant use of Xyrem and divalproex sodium is warranted.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Xyrem should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Oral administration of sodium oxybate to pregnant rats (150, 350, or 1,000 mg/kg/day) or rabbits (300, 600, or 1,200 mg/kg/day) throughout organogenesis produced no clear evidence of developmental toxicity. The highest doses tested in rats and rabbits were approximately 1 and 3 times, respectively, the maximum recommended human dose (MRHD) of 9 g per night on a body surface area (mg/m^2) basis.

Oral administration of sodium oxybate (150, 350, or 1,000 mg/kg/day) to rats throughout pregnancy and lactation resulted in increased stillbirths and decreased offspring postnatal viability and body weight gain at the highest dose tested. The no-effect dose for pre- and post-natal developmental toxicity in rats is less than the MRHD on a mg/m^2 basis.

8.2 Labor and Delivery

Xyrem has not been studied in labor or delivery. In obstetric anesthesia using an injectable formulation of sodium oxybate, newborns had stable cardiovascular and respiratory measures but were very sleepy, causing a slight decrease in Apgar scores. There was a fall in the rate of uterine contractions 20 minutes after injection. Placental transfer is rapid, but umbilical vein levels of sodium oxybate were no more than 25% of the maternal concentration. No sodium oxybate was detected in the infant's blood 30 minutes after delivery. Elimination curves of sodium oxybate between a 2-day-old infant and a 15-year-old patient were similar. Subsequent effects of sodium oxybate on later growth, development, and maturation in humans are unknown.

8.3 Nursing Mothers

It is not known whether sodium oxybate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Xyrem is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of Xyrem in patients with narcolepsy did not include sufficient numbers of subjects age 65 years and older to determine whether they respond differently from younger subjects. In controlled trials in another population, 39 (5%) of 874 patients were 65 years or older. Discontinuations of treatment due to adverse reactions were increased in the elderly compared to younger adults (20.5% v. 18.9%). Frequency of headaches was markedly increased in the elderly (38.5% v. 18.9%). The most common adverse reactions were similar in both age categories. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Hepatic Impairment

The starting dose of Xyrem should be reduced by one-half in patients with liver impairment *[see Dosage and Administration (2.3)* and *Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Xyrem is a Schedule III controlled substance under the Federal Controlled Substances Act. Non-medical use of Xyrem could lead to penalties assessed under the higher Schedule I controls.

9.2 Abuse

Xyrem (sodium oxybate), the sodium salt of GHB, produces dose-dependent central nervous system effects, including hypnotic and positive subjective reinforcing effects. The onset of effect is rapid, enhancing its potential for abuse or misuse.

The rapid onset of sedation, coupled with the amnestic features of Xyrem, particularly when combined with alcohol, has proven to be dangerous for the voluntary and involuntary user (e.g., assault victim).

Illicit GHB is abused in social settings primarily by young adults. Some of the doses estimated to be abused are in a similar dosage range to that used for treatment of patients with cataplexy. GHB has some commonalities with ethanol over a limited dose range, and some cross tolerance with ethanol has been reported as well. Cases of severe dependence and craving for GHB have been reported when the drug is taken around the clock. Patterns of abuse indicative of dependence include: 1) the use of increasingly large doses, 2) increased frequency of use, and 3) continued use despite adverse consequences.

Because illicit use and abuse of GHB have been reported, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of GHB (e.g. increase in size or frequency of dosing, drug-seeking behavior, feigned cataplexy). Dispose of Xyrem according to state and federal regulations. It is safe to dispose of Xyrem down the sanitary sewer.

9.3 Dependence

There have been case reports of withdrawal, ranging from mild to severe, following discontinuation of illicit use of GHB at frequent repeated doses (18 g to 250 g per day) in excess of the therapeutic dose range. Signs and symptoms of GHB withdrawal following abrupt discontinuation included insomnia, restlessness, anxiety, psychosis, lethargy, nausea, tremor, sweating, muscle cramps, tachycardia, headache, dizziness, rebound fatigue and sleepiness, confusion, and, particularly in the case of severe withdrawal, visual hallucinations, agitation, and delirium. These symptoms generally abated in 3 to 14 days. In cases of severe withdrawal, hospitalization may be required. The discontinuation effects of Xyrem have not been systematically evaluated in controlled clinical trials. In the clinical trial experience with Xyrem in narcolepsy/cataplexy patients at therapeutic doses, two patients reported anxiety and one reported insomnia following abrupt discontinuation at the termination of the clinical trial; in the two patients with anxiety, the frequency of cataplexy had increased markedly at the same time.

Tolerance

Tolerance to Xyrem has not been systematically studied in controlled clinical trials. There have been some case reports of symptoms of tolerance developing after illicit use at dosages far in excess of the recommended Xyrem dosage regimen. Clinical studies of sodium oxybate in the treatment of alcohol withdrawal suggest a potential cross-tolerance with alcohol. The safety and effectiveness of Xyrem in the treatment of alcohol withdrawal have not been established.

10 OVERDOSAGE

10.1 Human Experience

Information regarding overdose with Xyrem is derived largely from reports in the medical literature that describe symptoms and signs in individuals who have ingested GHB illicitly. In these circumstances the co-ingestion of other drugs and alcohol was common, and may have influenced the presentation and severity of clinical manifestations of overdose.

In clinical trials two cases of overdose with Xyrem were reported. In the first case, an estimated dose of 150 g, more than 15 times the maximum recommended dose, caused a patient to be unresponsive with brief periods of apnea and to be incontinent of urine and feces. This individual recovered without sequelae. In the second case, death was reported following a multiple drug overdose consisting of Xyrem and numerous other drugs.

10.2 Signs and Symptoms

Information about signs and symptoms associated with overdosage with Xyrem derives from reports of its illicit use. Patient presentation following overdose is influenced by the dose ingested, the time since ingestion, the co-ingestion of other drugs and alcohol, and the fed or fasted state. Patients have exhibited varying degrees of depressed consciousness that may fluctuate rapidly between a confusional, agitated combative state with ataxia and coma. Emesis (even when obtunded), diaphoresis, headache, and impaired psychomotor skills have been observed. No typical pupillary changes have been described to assist in diagnosis; pupillary reactivity to light is maintained. Blurred vision has been reported. An increasing depth of coma has been observed at higher doses. Myoclonus and tonic-clonic seizures have been reported. Respiration may be unaffected or compromised in rate and depth. Cheyne-Stokes respiration and apnea have been observed. Bradycardia and hypothermia may accompany

unconsciousness, as well as muscular hypotonia, but tendon reflexes remain intact.

10.3 Recommended Treatment of Overdose

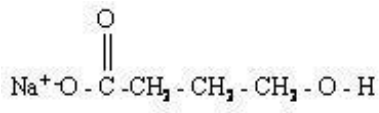
General symptomatic and supportive care should be instituted immediately, and gastric decontamination may be considered if co-ingestants are suspected. Because emesis may occur in the presence of obtundation, appropriate posture (left lateral recumbent position) and protection of the airway by intubation may be warranted. Although the gag reflex may be absent in deeply comatose patients, even unconscious patients may become combative to intubation, and rapid-sequence induction (without the use of sedative) should be considered. Vital signs and consciousness should be closely monitored. The bradycardia reported with GHB overdose has been responsive to atropine intravenous administration. No reversal of the central depressant effects of Xyrem can be expected from naloxone or flumazenil administration. The use of hemodialysis and other forms of extracorporeal drug removal have not been studied in GHB overdose. However, due to the rapid metabolism of sodium oxybate, these measures are not warranted.

10.4 Poison Control Center

As with the management of all cases of drug overdosage, the possibility of multiple drug ingestion should be considered. The healthcare provider is encouraged to collect urine and blood samples for routine toxicologic screening, and to consult with a regional poison control center (1-800-222-1222) for current treatment recommendations.

11 DESCRIPTION

Sodium oxybate, a CNS depressant, is the active ingredient in Xyrem. The chemical name for sodium oxybate is sodium 4-hydroxybutyrate. The molecular formula is $C_4H_7NaO_3$, and the molecular weight is 126.09 g/mole. The chemical structure is:



Sodium oxybate is a white to off-white, crystalline powder that is very soluble in aqueous solutions. Each mL of Xyrem contains 0.5 g of sodium oxybate in USP Purified Water, neutralized to pH 7.5 with malic acid.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Xyrem is a CNS depressant. The mechanism of action of Xyrem in the treatment of narcolepsy is unknown. Sodium oxybate is the sodium salt of gamma hydroxybutyrate, an endogenous compound and metabolite of the neurotransmitter GABA. It is hypothesized that the therapeutic effects of Xyrem on cataplexy and excessive daytime sleepiness are mediated through $GABA_B$ actions at noradrenergic and dopaminergic neurons, as well as at thalamocortical neurons.

12.3 Pharmacokinetics

Pharmacokinetics of sodium oxybate are nonlinear and are similar following single or repeat dosing.

Absorption

Following oral administration, sodium oxybate is absorbed rapidly across the clinical dose range, with

an absolute bioavailability of about 88%. The average peak plasma concentrations (C_{max}) following administration of each of the two 2.25 g doses given under fasting conditions 4 hours apart were similar. The average time to peak plasma concentration (T_{max}) ranged from 0.5 to 1.25 hours. Following oral administration, the plasma levels of sodium oxybate increased more than dose-proportionally, with blood levels increasing 3.7-fold as total daily dose is doubled from 4.5 g to 9 g. Single doses greater than 4.5 g have not been studied. Administration of Xyrem immediately after a high-fat meal resulted in delayed absorption (average T_{max} increased from 0.75 hr to 2 hr) and a reduction in C_{max} by a mean of 59% and of systemic exposure (AUC) by 37%.

Distribution

Sodium oxybate is a hydrophilic compound with an apparent volume of distribution averaging 190 mL/kg to 384 mL/kg. At sodium oxybate concentrations ranging from 3 mcg/mL to 300 mcg/mL, less than 1% is bound to plasma proteins.

Metabolism

Animal studies indicate that metabolism is the major elimination pathway for sodium oxybate, producing carbon dioxide and water via the tricarboxylic acid (Krebs) cycle and secondarily by beta-oxidation. The primary pathway involves a cytosolic $NADP^+$-linked enzyme, GHB dehydrogenase, that catalyzes the conversion of sodium oxybate to succinic semialdehyde, which is then biotransformed to succinic acid by the enzyme succinic semialdehyde dehydrogenase. Succinic acid enters the Krebs cycle where it is metabolized to carbon dioxide and water. A second mitochondrial oxidoreductase enzyme, a transhydrogenase, also catalyzes the conversion to succinic semialdehyde in the presence of α-ketoglutarate. An alternate pathway of biotransformation involves β-oxidation via 3,4-dihydroxybutyrate to carbon dioxide and water. No active metabolites have been identified.

Elimination

The clearance of sodium oxybate is almost entirely by biotransformation to carbon dioxide, which is then eliminated by expiration. On average, less than 5% of unchanged drug appears in human urine within 6 to 8 hours after dosing. Fecal excretion is negligible. Sodium oxybate has an elimination half-life of 0.5 to 1 hour.

Specific Populations

Geriatric

There is limited experience with Xyrem in the elderly. Results from a pharmacokinetic study (n=20) in another studied population indicate that the pharmacokinetic characteristics of sodium oxybate are consistent among younger (age 48 to 64 years) and older (age 65 to 75 years) adults.

Pediatric

The pharmacokinetics of sodium oxybate in patients younger than 18 years of age have not been studied.

Gender

In a study of 18 female and 18 male healthy adult volunteers, no gender differences were detected in the pharmacokinetics of sodium oxybate oral solution following a single oral dose of 4.5 g.

Race

There are insufficient data to evaluate any pharmacokinetic differences among races.

Renal Impairment

No pharmacokinetic study in patients with renal impairment has been conducted.

Hepatic Impairment

The pharmacokinetics of Xyrem in 16 cirrhotic patients, half without ascites (Child's Class A) and half with ascites (Child's Class C), were compared to the kinetics in 8 subjects with normal hepatic function

after a single oral dose of 25 mg/kg. AUC values were double in the cirrhotic patients, with apparent oral clearance reduced from 9.1 mL/min/kg in healthy adults to 4.5 and 4.1 mL/min/kg in Class A and Class C patients, respectively. Elimination half-life was significantly longer in Class C and Class A patients than in control patients (mean $t_{1/2}$ of 59 and 32 minutes, respectively, versus 22 minutes). The starting dose of Xyrem should be reduced by one-half in patients with liver impairment *[see Dosage and Administration (2.3); Use in Specific Populations (8.6)]*.

Drug Interactions Studies

Studies *in vitro* with pooled human liver microsomes indicate that sodium oxybate does not significantly inhibit the activities of the human isoenzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A up to the concentration of 3 mM (378 mcg/mL), a level considerably higher than levels achieved with therapeutic doses.

Drug interaction studies in healthy adults (age 18 to 50 years) were conducted with Xyrem and divalproex sodium, diclofenac, and ibuprofen:

- Divalproex sodium: Co-administration of Xyrem (6 g per day as two equal doses of 3 grams dosed four hours apart) with divalproex sodium (valproic acid, 1250 mg per day) increased mean systemic exposure to sodium oxybate as shown by AUC by approximately 25%, while C_{max} was comparable. Co-administration did not appear to affect the pharmacokinetics of valproic acid. A greater impairment on some tests of attention and working memory was observed with co-administration of both drugs than with either drug alone *[see Drug Interactions (7.2)* and *Dosage and Administration (2.4)]*.
- Diclofenac: Co-administration of Xyrem (6 g per day as two equal doses of 3 grams dosed four hours apart) with diclofenac (50 mg/dose twice per day) showed no significant differences in systemic exposure to sodium oxybate. Co-administration did not appear to affect the pharmacokinetics of diclofenac.
- Ibuprofen: Co-administration of Xyrem (6 g per day as two equal doses of 3 grams dosed four hours apart) with ibuprofen (800 mg/dose four times per day also dosed four hours apart) resulted in comparable systemic exposure to sodium oxybate as shown by plasma C_{max} and AUC values. Co-administration did not affect the pharmacokinetics of ibuprofen.

Drug interaction studies in healthy adults demonstrated no pharmacokinetic interactions between sodium oxybate and protriptyline hydrochloride, zolpidem tartrate, and modafinil. Also, there were no pharmacokinetic interactions with the alcohol dehydrogenase inhibitor fomepizole. However, pharmacodynamic interactions with these drugs cannot be ruled out. Alteration of gastric pH with omeprazole produced no significant change in the oxybate kinetics. In addition, drug interaction studies in healthy adults demonstrated no pharmacokinetic or clinically significant pharmacodynamic interactions between sodium oxybate and the SNRI duloxetine HCl.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Administration of sodium oxybate to rats at oral doses of up to 1,000 mg/kg/day for 83 (males) or 104 (females) weeks resulted in no increase in tumors. Plasma exposure (AUC) at the highest dose tested was 2 times that in humans at the maximum recommended human dose (MRHD) of 9 g per night.

The results of 2-year carcinogenicity studies in mouse and rat with gamma-butyrolactone, a compound that is metabolized to sodium oxybate *in vivo*, showed no clear evidence of carcinogenic activity. The plasma AUCs of sodium oxybate achieved at the highest doses tested in these studies were less than that in humans at the MRHD.

Mutagenesis

Sodium oxybate was negative in the *in vitro* bacterial gene mutation assay, an *in vitro* chromosomal aberration assay in mammalian cells, and in an *in vivo* rat micronucleus assay.

Impairment of Fertility

Oral administration of sodium oxybate (150, 350, or 1,000 mg/kg/day) to male and female rats prior to and throughout mating and continuing in females through early gestation resulted in no adverse effects on fertility. The highest dose tested is approximately equal to the MRHD on a mg/m^2 basis.

14 CLINICAL STUDIES

14.1 Cataplexy in Narcolepsy

The effectiveness of Xyrem in the treatment of cataplexy was established in two randomized, double-blind, placebo-controlled, multicenter, parallel-group trials (Trials N1 and N2) in patients with narcolepsy (see Table 4). In Trials N1 and N2, 85% and 80% of patients, respectively, were also being treated with CNS stimulants. The high percentages of concomitant stimulant use make it impossible to assess the efficacy and safety of Xyrem independent of stimulant use. In each trial, the treatment period was 4 weeks and the total nightly Xyrem doses ranged from 3 g to 9 g, with the total nightly dose administered as two equal doses. The first dose each night was taken at bedtime and the second dose was taken 2.5 to 4 hours later. There were no restrictions on the time between food consumption and dosing.

Trial N1 enrolled 136 narcoleptic patients with moderate to severe cataplexy (median of 21 cataplexy attacks per week) at baseline. Prior to randomization, medications with possible effects on cataplexy were withdrawn, but stimulants were continued at stable doses. Patients were randomized to receive placebo, Xyrem 3 g per night, Xyrem 6 g per night, or Xyrem 9 g per night.

Trial N2 was a randomized withdrawal trial with 55 narcoleptic patients who had been taking open-label Xyrem for 7 to 44 months prior to study entry. To be included, patients were required to have a history of at least 5 cataplexy attacks per week prior to any treatment for cataplexy. Patients were randomized to continued treatment with Xyrem at their stable dose (ranging from 3 g to 9 g per night) or to placebo for 2 weeks. Trial N2 was designed specifically to evaluate the continued efficacy of sodium oxybate after long-term use.

The primary efficacy measure in Trials N1 and N2 was the frequency of cataplexy attacks.

Table 4

Median Number of Cataplexy Attacks in Trials N1 and N2

Trial/Dosage Group	**Baseline**	**Median Change from Baseline**	**Comparison to Placebo (p-value)**
Trial N1 (Prospective, Randomized, Parallel Group Trial)			
		(median attacks/week)	
Placebo (n=33)	20.5	-4	–
Xyrem 6 g per night (n=31)	23.0	-10	0.0451
Xyrem 9 g per night (n=33)	23.5	-16	0.0016
Trial N2 (Randomized Withdrawal Trial)			
		(median attacks/2 weeks)	
Placebo (n=29)	4.0	21	–
Xyrem (n=26)	1.9	0	< 0.001

In Trial N1, both the 6 g and 9 g per night Xyrem doses resulted in statistically significant reductions in the frequency of cataplexy attacks. The 3 g per night dose had little effect. In Trial N2, patients randomized to placebo after discontinuing long-term open-label Xyrem therapy experienced a significant increase in cataplexy attacks ($p < 0.001$), providing evidence of long-term efficacy of Xyrem. In Trial N2, the response was numerically similar for patients treated with doses of 6 g to 9 g per night, but there was no effect seen in patients treated with doses less than 6 g per night, suggesting little effect at these doses.

14.2 Excessive Daytime Sleepiness in Narcolepsy

The effectiveness of Xyrem in the treatment of excessive daytime sleepiness in patients with narcolepsy was established in two randomized, double-blind, placebo-controlled trials (Trials N3 and N4) (see Tables 5 to 7). Seventy-eight percent of patients in Trial N3 were also being treated with CNS stimulants.

Trial N3 was a multicenter randomized, double-blind, placebo-controlled, parallel-group trial that evaluated 228 patients with moderate to severe symptoms at entry into the study including a median Epworth Sleepiness Scale (see below) score of 18, and a Maintenance of Wakefulness Test (see below) score of 8.3 minutes. Patients were randomized to one of 4 treatment groups: placebo, Xyrem 4.5 g per night, Xyrem 6 g per night, or Xyrem 9 g per night. The period of double-blind treatment in this trial was 8 weeks. Antidepressants were withdrawn prior to randomization; stimulants were continued at stable doses.

The primary efficacy measures in Trial N3 were the Epworth Sleepiness Scale and the Clinical Global Impression of Change. The Epworth Sleepiness Scale is intended to evaluate the extent of sleepiness in everyday situations by asking the patient a series of questions. In these questions, patients were asked to rate their chances of dozing during each of 8 activities on a scale from 0-3 (0=never; 1=slight; 2=moderate; 3=high). Higher total scores indicate a greater tendency to sleepiness. The Clinical Global Impression of Change is evaluated on a 7-point scale, centered at *No Change*, and ranging from *Very Much Worse* to *Very Much Improved*. In Trial N3, patients were rated by evaluators who based their assessments on the severity of narcolepsy at baseline.

In Trial N3, statistically significant improvements were seen on the Epworth Sleepiness Scale score at Week 8 and on the Clinical Global Impression of Change score at Week 8 with the 6 g and 9 g per night doses of Xyrem compared to the placebo group.

Table 5

Change from Baseline in Daytime Sleepiness Score (Epworth Sleepiness Scale) at Week 8 in Trial N3 (Range 0-24)

Treatment Group	Baseline	Week 8	Median Change from Baseline at Week 8	p-value
Placebo (n=59)	17.5	17.0	-0.5	-
Xyrem 6 g per night (n=58)	19.0	16.0	-2.0	< 0.001
Xyrem 9 g per night (n=47)	19.0	12.0	-5.0	< 0.001

Table 6

Proportion of patients with a very much or much improved Clinical Global Impression of Change in Daytime and Nighttime Symptoms in Trial N3

Treatment Group	Percentages of Responders (Very Much Improved or Much Improved)	Change from Baseline Significance Compared to Placebo (p-value)
Placebo (59)	22%	-
Xyrem 6 g per night (n=58)	52%	< 0.001
Xyrem 9 g per night (n=47)	64%	< 0.001

Trial N4 was a multicenter randomized, double-blind, placebo-controlled, parallel-group trial that evaluated 222 patients with moderate to severe symptoms at entry into the study including a median Epworth Sleepiness Scale score of 15, and a Maintenance of Wakefulness Test (see below) score of 10.3 minutes. At entry, patients had to be taking modafinil at stable doses of 200 mg, 400 mg, or 600 mg daily for at least 1 month prior to randomization. The patients enrolled in the study were randomized to one of 4 treatment groups: placebo, Xyrem, modafinil, or Xyrem plus modafinil. Xyrem was administered in a dose of 6 g per night for 4 weeks, followed by 9 g per night for 4 weeks. Modafinil was continued in the modafinil alone and the Xyrem plus modafinil treatment groups at the patient's prior dose. Trial N4 was not designed to compare the effects of Xyrem to modafinil because patients receiving modafinil were not titrated to a maximal dose. Patients randomized to placebo or to Xyrem treatment were withdrawn from their stable dose of modafinil. Patients taking antidepressants could continue these medications at stable doses.

The primary efficacy measure in Trial N4 was the Maintenance of Wakefulness Test. The Maintenance of Wakefulness Test measures latency to sleep onset (in minutes) averaged over 4 sessions at 2-hour intervals following nocturnal polysomnography. For each test session, the subject was asked to remain awake without using extraordinary measures. Each test session is terminated after 20 minutes if no sleep occurs, or after 10 minutes, if sleep occurs. The overall score is the mean sleep latency for the 4 sessions.

In Trial N4, a statistically significant improvement in the change in the Maintenance of Wakefulness Test score from baseline at Week 8 was seen in the Xyrem and Xyrem plus modafinil groups compared to the placebo group.

This trial was not designed to compare the effects of Xyrem to modafinil, because patients receiving modafinil were not titrated to a maximally effective dose.

Table 7

Change in Baseline in the Maintenance of Wakefulness Test Score (in minutes) at Week 8 in Trial N4

Treatment Group	Baseline	Week 8	Mean Change from Baseline at Week 8	p-value
Placebo (modafinil withdrawn) (n=55)	9.7	6.9	-2.7	-
Xyrem (modafinil withdrawn) (n=50)	11.3	12.0	0.6	< 0.001
Xyrem plus modafinil (n=54)	10.4	13.2	2.7	< 0.001

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Xyrem is a clear to slightly opalescent oral solution. Each prescription includes a carton containing one bottle of Xyrem, a press-in-bottle-adaptor, an oral measuring device (plastic syringe), and a Medication

Guide. The pharmacy provides two empty vials with child-resistant caps with each Xyrem shipment.

Each amber bottle contains Xyrem oral solution at a concentration of 0.5 g per mL and has a child-resistant cap.

Carton containing one 180 mL bottle NDC 68727-100-01

16.2 Storage

Keep out of reach of children.

Xyrem should be stored at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) (see USP Controlled Room Temperature).

Dispense in tight containers.

Solutions prepared following dilution should be consumed within 24 hours.

16.3 Handling and Disposal

Xyrem is a Schedule III drug under the Controlled Substances Act. Xyrem should be handled according to state and federal regulations. It is safe to dispose of Xyrem down the sanitary sewer.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Xyrem REMS Program

Inform patients that Xyrem is available only through a restricted distribution program called the Xyrem REMS Program.

The contents of the Xyrem Medication Guide and educational materials are reviewed with every patient before initiating treatment with Xyrem.

Patients must read and understand the materials in the Xyrem REMS Program prior to initiating treatment. Inform the patient that they should be seen by the prescriber frequently to review dose titration, symptom response, and adverse reactions; a follow-up of every three months is recommended.

Discuss safe and proper use of Xyrem and dosing information with patients prior to the initiation of treatment. Instruct patients to store Xyrem bottles and Xyrem doses in a secure place, out of the reach of children and pets.

Alcohol or Sedative Hypnotics

Advise patients not to drink alcohol or take other sedative hypnotics if they are taking Xyrem.

Sedation

Inform patients that after taking Xyrem they are likely to fall asleep quickly (often within 5 and usually within 15 minutes), but the time it takes to fall asleep can vary from night to night. The sudden onset of sleep, including in a standing position or while rising from bed, has led to falls complicated by injuries, in some cases requiring hospitalization. Instruct patients to remain in bed following ingestion of the first and second doses. Instruct patients not to take their second dose until 2.5 to 4 hours after the first dose.

Food Effects on Xyrem

Inform patients to take the first dose at least 2 hours after eating.

Respiratory Depression

Inform patients that Xyrem can be associated with respiratory depression.

Operating Hazardous Machinery

Inform patients that until they are reasonably certain that Xyrem does not affect them adversely (e.g., impair judgment, thinking, or motor skills) they should not operate hazardous machinery, including automobiles or airplanes.

Suicidality

Instruct patients or families to contact a healthcare provider immediately if the patient develops depressed mood, markedly diminished interest or pleasure in usual activities, significant change in weight and/or appetite, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, or suicidal ideation.

Sleepwalking

Instruct patients and their families that Xyrem has been associated with sleepwalking and to contact their healthcare provider if this occurs.

Sodium Intake

Instruct patients who are sensitive to salt intake (e.g., those with heart failure, hypertension, or renal impairment) that Xyrem contains a significant amount of sodium and they should limit their sodium intake.

Distributed By:

Jazz Pharmaceuticals, Inc.
Palo Alto, CA 94304

Protected by U.S. Patent Nos. 6,472,431; 6,780,889; 7,262,219; 7,851,506; 8,263,650; 8,324,275; 8,461,203; 8,772,306; 8,859,619; 8,952,062

MEDICATION GUIDE

Xyrem® (ZĪE-rem)

(sodium oxybate)

oral solution CIII

Read this Medication Guide carefully before you start taking Xyrem and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment.

What is the most important information I should know about Xyrem?

Xyrem can cause serious side effects including slow breathing or changes in your alertness. Do not drink alcohol or take medicines intended to make you fall asleep while you are taking Xyrem because they can make these side effects worse. Call your doctor right away if you have any of these serious side effects.

- The active ingredient of Xyrem is a form of gamma-hydroxybutyrate (GHB). GHB is a chemical that has been abused and misused. Abuse and misuse of Xyrem can cause serious medical problems, including:
    - seizures
    - trouble breathing
    - changes in alertness
    - coma
    - death

- Do not drive a car, use heavy machinery, fly an airplane, or do anything that is dangerous or that requires you to be fully awake for at least 6 hours after you take Xyrem. You should not do those activities until you know how Xyrem affects you.
- Xyrem is available only by prescription and filled through the central pharmacy in the Xyrem REMS Program. Before you receive Xyrem, your doctor or pharmacist will make sure that you understand how to use Xyrem safely and effectively. If you have any questions about Xyrem, ask your doctor or call the Xyrem REMS Program at 1-866-997-3688.

What is Xyrem?

Xyrem is a prescription medicine used to treat the following symptoms in people who fall asleep frequently during the day, often at unexpected times (narcolepsy):

- suddenly weak or paralyzed muscles when they feel strong emotions (cataplexy)
- excessive daytime sleepiness (EDS) in people who have narcolepsy

It is not known if Xyrem is safe and effective in children.

Xyrem is a controlled substance (CIII) because it contains sodium oxybate that can be a target for people who abuse prescription medicines or street drugs. Keep your Xyrem in a safe place to protect it from theft. Never give your Xyrem to anyone else because it may cause death or harm them. Selling or giving away this medicine is against the law.

Who should not take Xyrem?

Do not take Xyrem if you:

- take other sleep medicines or sedatives (medicines that cause sleepiness)
- drink alcohol
- have a rare problem called succinic semialdehyde dehydrogenase deficiency

Before you take Xyrem, tell your doctor if you:

- have short periods of not breathing while you sleep (sleep apnea)
- snore, have trouble breathing, or have lung problems. You may have a higher chance of having serious breathing problems when you take Xyrem.
- have or had depression or have tried to harm yourself. You should be watched carefully for new symptoms of depression.
- have liver problems
- are on a salt-restricted diet. Xyrem contains a lot of sodium (salt) and may not be right for you.
- have high blood pressure
- have heart failure
- have kidney problems
- are pregnant or plan to become pregnant. It is not known if Xyrem can harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if Xyrem passes into your breast milk. You and your doctor should decide if you will take Xyrem or breastfeed.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Especially, tell your doctor if you take other medicines to help you sleep (sedatives). Do not take medicines that make you sleepy with Xyrem.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take Xyrem?

- Read the **Instructions for Use** at the end of this Medication Guide for detailed instructions on how to take Xyrem.
- Take Xyrem exactly as your doctor tells you to take it.
- Never change your Xyrem dose without talking to your doctor.
- Xyrem can cause sleep very quickly. You should fall asleep soon. Some patients fall asleep within 5 minutes and most fall asleep within 15 minutes. Some patients take less time to fall asleep and some take more time. The time it takes you to fall asleep might be different from night to night.
- Take your first Xyrem dose at bedtime while you are in bed. Take your second Xyrem dose 2 ½ to 4 hours after you take your first Xyrem dose. You may want to set an alarm clock to make sure you wake up to take your second Xyrem dose. You should remain in bed after taking the first and second doses of Xyrem.
- If you miss your second Xyrem dose, skip that dose and do not take Xyrem again until the next night. Never take 2 Xyrem doses at 1 time.
- Wait at least 2 hours after eating before you take Xyrem.
- You should see your doctor every 3 months for a check-up while taking Xyrem. Your doctor should check to see if Xyrem is helping to lessen your symptoms and if you feel any side effects while you take Xyrem.
- If you take too much Xyrem, call your doctor or go to the nearest hospital emergency room right away.

What are the possible side effects of Xyrem?

Xyrem can cause serious side effects, including:

- See **"What is the most important information I should know about Xyrem?"**
- **Breathing problems, including:**
    - slower breathing
    - trouble breathing
    - short periods of not breathing while sleeping (sleep apnea). People who already have breathing or lung problems have a higher chance of having breathing problems when they use Xyrem.
- **Mental health problems, including:**
    - confusion
    - seeing or hearing things that are not real (hallucinations)
    - unusual or disturbing thoughts (abnormal thinking)
    - feeling anxious or upset
    - depression
    - thoughts of killing yourself or trying to kill yourself

Call your doctor right away if you have symptoms of mental health problems.

- **Sleepwalking.** Sleepwalking can cause injuries. Call your doctor if you start sleepwalking. Your doctor should check you.

The most common side effects of Xyrem include:

- nausea
- dizziness
- vomiting
- bedwetting
- diarrhea

Your side effects may increase when you take higher doses of Xyrem.

Xyrem can cause physical dependence and craving for the medicine when it is not taken as directed.

These are not all the possible side effects of Xyrem. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Xyrem?

- **Always store Xyrem in the original bottle or in pharmacy containers with child-resistant caps provided by the pharmacy.**
- **Keep Xyrem in a safe place out of the reach of children and pets.**
- **Get emergency medical help right away if a child drinks your Xyrem.**
- Store Xyrem between 68°F to 77°F (20°C to 24°C). When you have finished using a Xyrem bottle:
  - empty any unused Xyrem down the sink drain
  - cross out the label on the Xyrem bottle with a marker
  - place the empty Xyrem bottle in the trash

General information about the safe and effective use of Xyrem

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Xyrem for a condition for which it was not prescribed. Do not give Xyrem to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about Xyrem. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about Xyrem that is written for health professionals.

For more information, go to www.XYREMREMS.com or call the Xyrem REMS Program at 1-866-997-3688.

What are the ingredients in Xyrem?
Active Ingredients: sodium oxybate

Inactive Ingredients: purified water and malic acid

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Distributed By:

Jazz Pharmaceuticals, Inc.
Palo Alto, CA 94304

Revised: April 2015

Instructions for Use

Xyrem® (ZĪE-rem)

(sodium oxybate)

oral solution CIII

Read these Instructions for Use carefully before you start taking Xyrem and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment.

Note:

- **You will need to split your prescribed Xyrem dose into 2 separate pharmacy containers for mixing.**
- **You will need to mix Xyrem with water before you take your dose.**
- Take your dose within 24 hours after mixing Xyrem with water. If you do not take your dose within this time, you will need to throw the mixture away.

Supplies you will need for mixing and taking Xyrem: See Figure A.

- bottle of your Xyrem medicine
- press-in-bottle-adaptor with straw attached
- syringe for drawing up your Xyrem dose
- a measuring cup containing about ¼ cup of water (not provided with your Xyrem prescription)
- 2 **empty** pharmacy containers with child-resistant caps
- alarm clock by your bedside (alarm clock may be included in your first shipment of Xyrem)

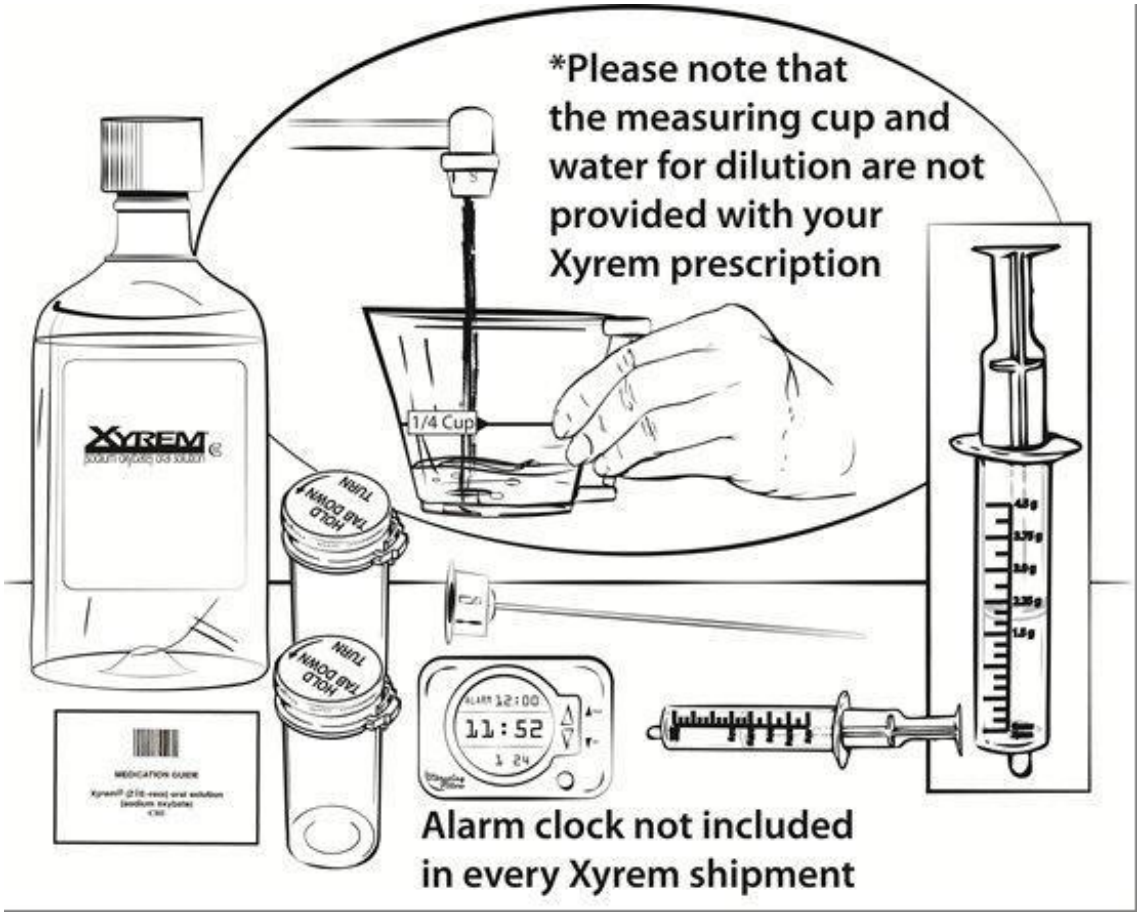


Figure A

Step 1. Take the Xyrem bottle, press-in-bottle-adaptor, and syringe out of the box.

Step 2. Remove the bottle cap from the Xyrem bottle by pushing down while turning the cap counterclockwise (to the left). See Figure B.

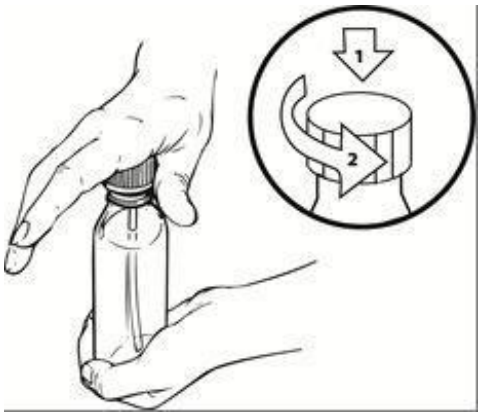


Figure B

Step 3.

- The press-in-bottle-adaptor may already be put in place by the pharmacy. If it is not already in place, you will have to do it yourself. After removing the cap from the Xyrem bottle, set the bottle upright on a tabletop.
- While holding the Xyrem bottle in its upright position, insert the press-in-bottle-adaptor into the

neck of the Xyrem bottle. See Figure C.

Figure C

- Tilt the straw toward the edge of the bottom of the bottle to be sure you can draw out your dose of the medicine. You only need to do this the first time you open the bottle. See Figure D.

Figure D

- After you draw out your dose of the medicine, leave the adaptor in the bottle for all your future uses. See Figure E.

Figure E

Step 4.

- Take the syringe out of the plastic wrapper. Use only the syringe provided with your Xyrem prescription.
- While holding the Xyrem bottle upright on the tabletop, insert the tip of the syringe into the opening on top of the Xyrem bottle and press down firmly. See Figure F.

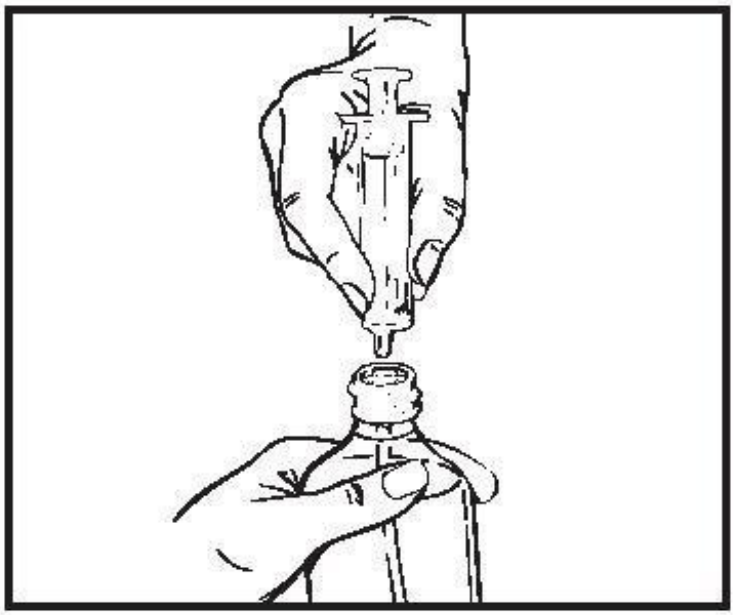


Figure F

Step 5.

- Hold the bottle and syringe down with one hand, and draw up one-half (1/2) of your total prescribed nightly dose with the other hand by pulling up on the plunger. For example, if your total nightly dose of Xyrem is 4.5 grams a night, you will need to draw up 2 separate doses of 2.25 grams each, one for each pharmacy container. See Figure G.

Note: **The Xyrem medicine will not flow into the syringe unless you keep the bottle upright.**

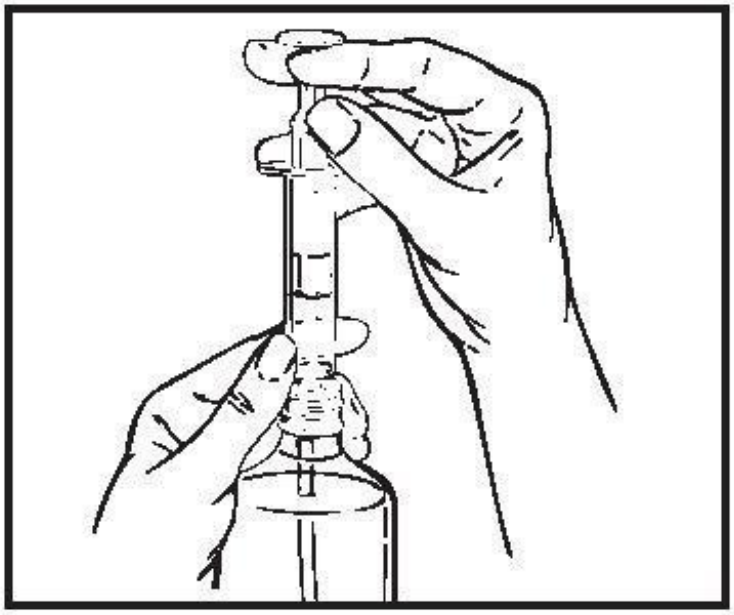


Figure G

Step 6.

- After you draw up each separate Xyrem dose, remove the syringe from the opening of the Xyrem bottle. Put the tip into 1 of the **empty** containers with child-resistant caps provided by the pharmacy.
- **Make sure the pharmacy container is empty and does not contain any medicine from your previous night's dose.**
    - Empty each separate Xyrem dose into 1 of the **empty** pharmacy containers by pushing down on the plunger. (See Figure H).
- Using a measuring cup, pour about ¼ cup of water into **each** container. **Be careful to add only water to each container and not more Xyrem. All shipped bottles of Xyrem contain the concentrated medicine. Water for mixing the medicine is not provided in the shipment.**

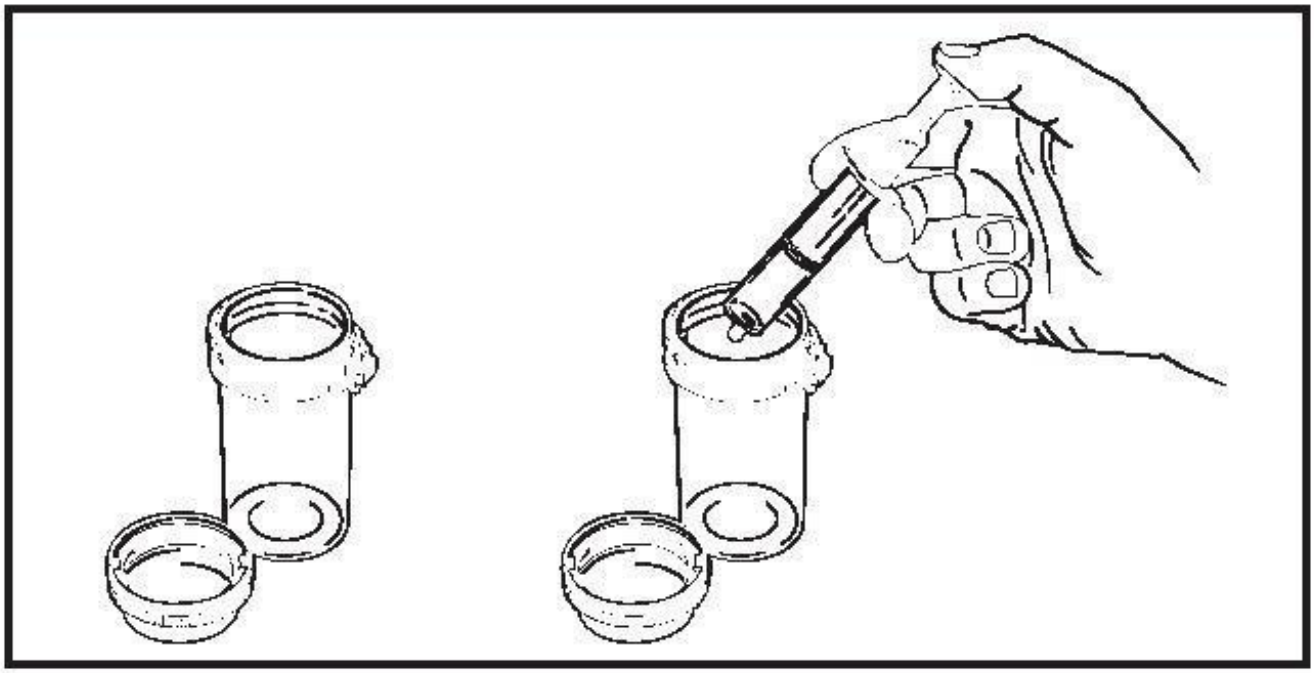


Figure H

Step 7.

- Place the child-resistant caps provided on the filled pharmacy containers and turn each cap clockwise (to the right) until it clicks and locks into its child-resistant position. See Figure I.

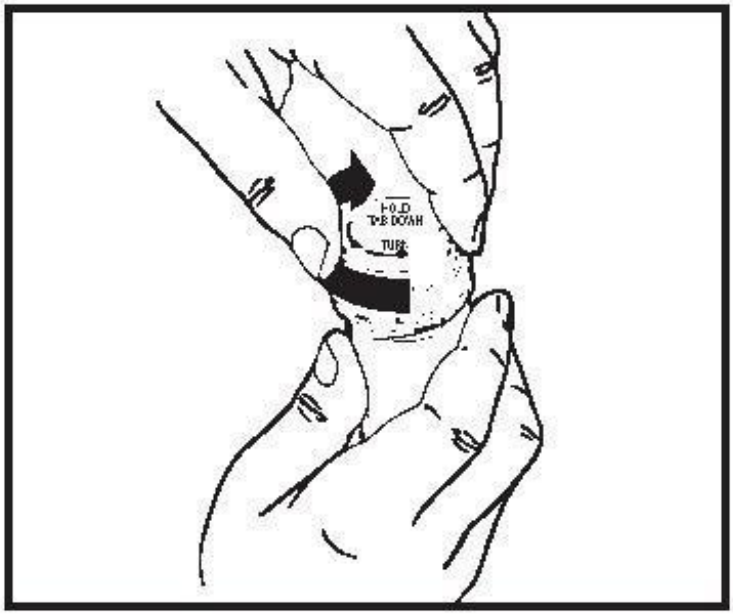


Figure I

- Put the cap back on the Xyrem bottle and store it in a safe and secure place. Store in a locked place if needed. Keep Xyrem out of the reach of children and pets.
- Rinse the syringe out with water and squirt the liquid into the sink drain.

Step 8.

- At bedtime, and before you take your first Xyrem dose, put your second Xyrem dose in a safe place near your bed.
- You may want to set an alarm clock to make sure you wake up to take the second dose.
- When it is time to take your first Xyrem dose, remove the cap from the container by pressing down on the child-resistant locking tab and turning the cap counterclockwise (to the left).
- Drink all of your first Xyrem dose at bedtime. Put the cap back on the first container before lying down to sleep.
- You should fall asleep soon. Some patients fall asleep within 5 minutes and most fall asleep within 15 minutes. Some patients take less time to fall asleep, and some take more time. The time it takes you to fall asleep might be different from night to night.

Step 9.

- When you wake up 2½ to 4 hours later, take the cap off the second pharmacy container.
- If you wake up before the alarm and it has been at least 2½ hours since your first Xyrem dose, turn off your alarm and take your second Xyrem dose.
- While sitting in bed, drink all of the second Xyrem dose and put the cap back on the second pharmacy container before lying down to continue sleeping.

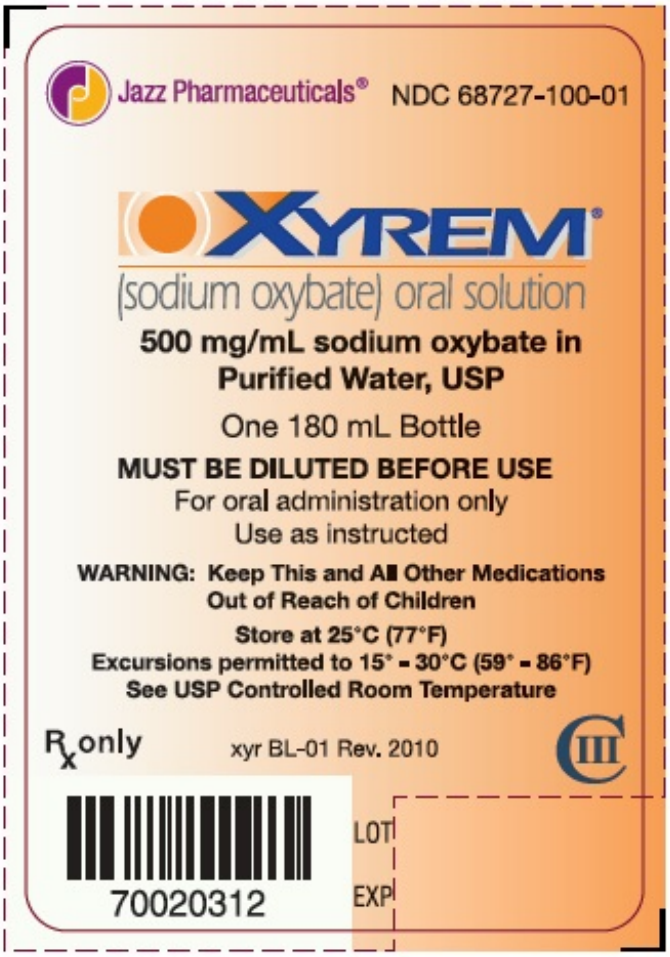
Distributed By:

Jazz Pharmaceuticals, Inc.
Palo Alto, CA 94304

These Instructions for Use have been approved by the U.S. Food and Drug Administration.

Revised: April 2015

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL



XYREM

sodium oxybate solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:68727-100
Route of Administration	ORAL	**DEA Schedule**	CIII

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
SODIUM OXYBATE (UNII: 7G33012534) (4-HYDROXYBUTANOIC ACID - UNII:30IW36W5B2)	SODIUM OXYBATE	0.5 g in 1 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68727-100-01	1 in 1 CARTON		
1		180 mL in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA021196	07/17/2002	

Labeler - Jazz Pharmaceuticals, Inc. (135926363)

Registrant - Jazz Pharmaceuticals, Inc. (135926363)

Establishment

Name	Address	ID/FEI	Business Operations
Jazz Pharmaceuticals, Inc.		135926363	MANUFACTURE(68727-100)

Revised: 4/2015 Jazz Pharmaceuticals, Inc.